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ASSISTANT COMMISSIONER FOR PATENTS

WASHINGTON, D.C. 20231

ATTENTION: BOX PATENT APPLICATION

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): **Reynolds Gorsuch and Henry Grage**

For: **SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION**

Enclosed are:

(X) 17 sheets of formal drawings.

(X) Petition to Submit Black and White Photo Drawings.

(X) Recordation form cover sheet with 2-page assignment.

(X) A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27.

(X) A power of attorney form and copy of assignment.

(X) Initial signed declaration by inventor(s).

(X) Return prepaid postcard.

CLAIMS AS FILED

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
Basic Fee			$345	$345
Total Claims	90 - 20 =	70×	$9	$630
Independent Claims	4 - 3 =	1 ×	$39	$39
If application contains any multiple dependent claims(s), then add			$130	$130
	TOTAL FILING FEE	$1,144		

(X) A check in the amount of $1,144 to cover the filing fee is enclosed.

(X) A check in the amount of $40.00 to cover the assignment recording fee.

(X) A check in the amount of $130.00 to cover the Petition to Submit Black and White Drawings is enclosed.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, now or in the future, or credit any overpayment to Account No. 11-1410. A duplicate copy of this sheet is enclosed.

(X) Please use Customer No. 20,995 for the correspondence address.

Jerry R. Seiler
Registration No. 23,051
Attorney of Record

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CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Attorney Docket No.	:	TRANSVI.007A
Applicant(s)	:	Gorsuch, et al.
For	:	SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION
Attorney	:	Jerry R. Seiler
"Express Mail" Mailing Label No.	:	EL501130147US
Date of Deposit	:	April 13, 2000

I hereby certify that the accompanying Transmittal in Duplicate; Specification in 16 pages; 17 sheets of drawings; **Signed** Declaration by Inventor in 2 pages; **Signed** Declaration and Power of Attorney in 2 pages; Recordation Form Cover Sheet and Assignment in 3 pages; Power of Attorney by Assignee in 2 pages; Small Entity Statement; Submission of Formal Drawings; Information Disclosure Statement, Checks for Filing Fees; and Return Prepaid Postcard are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Rose Flanagan

Rose Flanagan

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VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL-ENTITY STATUS

I, the undersigned, do hereby declare that:

[X] I am an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: TRANSVIVO, INC.
ADDRESS OF CONCERN: 1100 Lincoln Avenue, Suite 206, Napa, CA 94558

I further declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both. I further declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in the patent or application identified above.

The individual, concern or organization identified above has not assigned, granted, conveyed or licensed, and is under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

If the rights held by the above-identified individual, concern or organization are not exclusive, each individual, concern or organization having rights in the invention are identified below. Each such individual, concern or organization must file separate verified statements averring to their status as small entities.

***NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).**

FULL NAME:
ADDRESS:
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small-entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Jim Chestnut
TITLE OF PERSON (if not an owner or individual): President
ADDRESS OF PERSON SIGNING: 1100 Lincoln Avenue, Suite 206, Napa, CA 94558

SIGNATURE: ______________ DATE: 4-2-00

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SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION

Background of the Invention

In U.S. Patent Nos. 4,950,224, 5,152,743, 5,151,082, 5,735,809 and 5,980,478 there are disclosed methods and apparatus for carrying out *in-vivo* plasmapheresis for separating plasma from other blood components within the body and blood vessels of the patient. The apparatus uses pumping means to create a trans-membrane pressure (TMP) and motivate the flow of fluid from within the *in-vivo* system, whereby blood plasma is pumped from the patient to a treatment means such as a dialyzer apparatus in which toxic metabolic waste in the plasma is removed. After the plasma is treated for removal of waste products, excess fluids, toxins, and/or other deleterious plasma proteins, the treated plasma is returned and reintroduced to the patients' blood stream. Such methods are referred to as plasma dialysis, ultrafiltration or blood purification. The methods and apparatus described in the aforesaid patents are incorporated herein by reference.

These methods of toxin removal from blood as taught by the above patents are unique and substantially superior from conventional means of hemodialysis as presently practiced for both acute and chronic kidney failure, primarily because removal of whole blood from the patient's vasculature is eliminated from the procedure using plasma, or portions of the plasma instead. In conventional hemodialysis procedures hollow fiber membranes are used in the *ex-vivo* dialysis and hemofilter cartridges for blood purification. The blood is routed from the body through the center lumen of the hollow fibers in the cartridges and dialysate fluid is routed over the outside walls of the fibers within the cartridge cavity in counter-flow direction to blood flow. Thus, toxin diffusion and ultrafiltration are from inside the fiber lumen to a compartment outside the fiber walls where the ultrafiltrate and toxin-saturated dialysate are collected for further processing and/or disposal.

Conventional hollow fiber membranes commercially used for present hemodialysis, hemo-ultrafiltration, and dialyzer cartridges fabricated from proprietary

and non-proprietary polymer compositions generally utilize two types of morphologies: symmetrical and asymmetrical. In a symmetrical composition, the basic morphology or cellular structure and porosity of the fiber wall is uniform from the inner lumen to the outside surface. In asymmetrical compositions, both morphology and pore structures vary from the inner lumen to the outer surface to meet the high pressure requirements of the filter cartridges in which the TMP inside the fiber lumen is high (100 - 300 mmHg) while the blood flow itself in the fibers is near stagnant (2 - 300 ml/min/7,000 fibers = .042 ml/m/fiber). These commercial membranes generally also have poor structural strength, acceptable in an encapsulated device external to the body but which would not be acceptable for an *in-vivo* placement for safety reasons. Such conventional fiber membranes are not suitable for the demanding environment of the *in-vivo*, high blood flow (vena cava = 2.5 l/min), low TMP ($\leq$ 50 mmHg), and unencapsulated environment of plasma extraction devices described by the aforesaid patent applications.

Summary of the Invention

The present invention is directed to specialized hollow fiber membranes having the function of separation of plasma or a portion of the plasma from blood and having the unique morphology, performance properties and materials biocompatible characteristics necessary for effective and optimal utilization for *in-vivo* vascular implantation as the operating element in catheter-based devices as described in the aforesaid patents and other such similar devices for the separation and extraction of plasma and plasma components from the blood. The ultrafiltrate (exudate) may be transported *ex-vivo* via a catheter lumen where it is discarded, or treated by cascade filtration means, dialysis (solute diffusion) means, or other methods known to the art, and returned to the patient via a separate lumen in the catheter.

The hollow fiber membrane of the invention is tubular in shape and generally circular in cross-section, having a coaxial inner lumen along the length of the fiber in its center. The wall volume of the fibers is asymmetrical with a variable morphology from the outer diameter to that of the inner diameter, having a higher mass density at the outer wall and a lower mass density at the inner wall. The fibers are designed to facilitate ultrafiltration with the permeate outside the fibers and the exudate inside the

fibers. The inner lumen of all fibers in a fiber extraction assembly are in direct fluid communication with the access lumen of the catheter which provides means for transporting the exudate *ex- vivo*.

Brief Description of the Drawings

Figure 1 is a schematic end view of a hollow fiber illustrating the membrane morphology structure having four zones;

Figure 2 is a scanning electron microscopy (SEM) image of a cross-section of a portion of the fiber of the invention at 400 μm magnification showing four zones of the asymmetrical wall structure between the inner and outer fiber wall surfaces;

Figure 3 shows a portion of a cross-section of a portion of the fiber at a magnification of 5,000 μm;

Figure 4 is a SEM cross-section of Zones 1, 2 and 3 of the fiber shown in Figure 2 at a magnification of 1,000 μm;

Figure 5 is a SEM cross-section of Zones 3 and 4 of the fiber shown in Figure 2 at a magnification of 1,000 μm;

Figure 6 shows a transverse view of the inner lumen wall of the fiber at a magnification of 5,000 μm; and

Figure 7 is a graph illustrating the hollow fiber membrane sieving coefficient curves.

Detailed Description of the Preferred Embodiment

As illustrated in Figures 1-5, the features of the fiber wall of the membrane of the invention include a pore and void structure defined within frames or solid walls which form boundaries of the pores. The pores are voids of variable definitive sizes which permit passage of fluid through the fiber wall to the lumen and which pores obstruct the passage of components larger than the pore diameter. As illustrated particularly in Figure 3, the pores are irregular-shaped voids bounded by solid frames to form irregular tortuous paths for irregular and regular-shaped solutes. The wall structure of the fiber from the outer surface to the lumen is a continuum with non-linear pore and void distribution. The resulting structure is a continuous change in mass

density between the outer surface of the fiber and the inner lumen surface. Thus, it is convenient to describe these changes in mass density as sections of the wall area having an average nominal pore size, porosity and wall mass in terms of zones with macro-functions.

In Figure 1, the wall structure illustrated has four zone sections, each zone characterized by a different mass pore density based on the average nominal pore size in the respective zones. The section of Zone 1 is adjacent to the fiber outer surface or outer diameter. Zone 1 forms the fiber interface with the permeate blood flow and although being the thinnest zone contains the highest density of operationally controlling pores for the fiber membrane performance. Thus, Zone 1 has the principal effect in the filtration process for controlling the trans-membrane flux (TMF) which is dependent on pore size, porosity and virtual membrane thickness.

The section of Zone 2, while having some flux-controlling pores, is principally a structural member for providing strength to the fiber as well as acting as a conduit for exudate flow to the section of Zone 3. The latter is principally a structural member with expanded pores for reducing the hydraulic resistance and providing a fluid conduit to the lumen of the fiber, and thus, in the example, as shown, has little filtration function. The section of Zone 4 has very large voids and pores with very little solid structure, thereby having the primary function of a major reduction of hydraulic resistance through the membrane and defining the fiber inner lumen diameter surface.

Figure 2 illustrates a cross-section of the fiber wall showing the structure of Zones 1-4 at 400 μm magnification. The fiber wall morphology demonstrates the continuum of expanding plurosity and open spaces from the virtual control pore size of Zone 1 adjacent to the outer fiber diameter to the very open and low-flow resistant structure in Zone 4 adjacent to the inner lumen wall.

Figure 3, a cross-section of Zone 1 at a magnification of 5,000 μm, shows pores and their boundary solid wall frames and the high uniformity of pore geometry and diverse irregular shapes of the individual pore dimensions. It is this high uniformity of pore size and high porosity as well as the thinness of Zone 1 which produces the high separation efficiency and high TMF of the membrane.

Figure 4 shows a cross-section of Zones 1, 2 and 3 at a magnification of 1,000 μm to illustrate the transition of the high-density structure of Zone 1 in comparison to the more open densities of Zones 2 and 3, as well as the uniformity and continuity of fiber structure producing high tensile and elongation strength.

Figure 5, also at a magnification of 1,000 μm, shows the structure of Zones 3 and 4 to illustrate the rapidly expanding open spaces and fluid communication channels which produce the lowered hydraulic resistance to flow of the exudate and results in a very high TMF as a function of a very low TMP.

Figure 6 is a 5,000 μm magnification of a transverse view of the inner lumen wall showing the highly open but contiguous nature of the structure at that site, facilitating fluid communication of the exudate from the flow through the fiber to the fiber lumen.

Figure 7 illustrates a sieving coefficient curve to provide a measure of membrane performance *in-situ* in an operating environment. The sieving coefficient curves illustrated are determined or generated by measuring the amount of a series of specific solutes or proteins in exudate passed through the membrane by convection as a percentage of the amount of the permeate of the same solute or protein in the blood. The vertical axis of the chart illustrated is linear from 0 to 100% and the horizontal axis is semi-logarithmic in two scales; the first scale is expressed in pore size in μm; the second scale is expressed in the molecular weight of the solute in Daltons. Curve 10 of Figure 7 represents the typical curve of a plasma extraction membrane with exudate performance in Areas A and B. Curve 11 shows the typical exudate performance of a hemofilter (ultrafiltration) membrane with exudate performance in Area B, wherein Areas A plus B plus C constitute all components of the blood. Thus, Curve 10 represents the typical sieving coefficient curve for membranes with pores in the 0.3 to 0.7 μm diameter size, as used in plasmapheresis while Curve 11 represents a typical sieving coefficient curve for membranes with pores in the 0.006 to 0.009 μm diameter size used for ultrafiltration.

The driving force for convective transport of the plasma fluid and solutes is the TMF equal to P_f x TMP (and linear below the critical flow limit) where P_f is the hydraulic permeability of the membrane, and:

P_f = $(n \pi r_p^4) / (\tau \mu \Delta x)$ Where:

(n) = Porosity (number of pores/unit area)

(π) = 3.14159

(r_p) = Pore radius (pore size)

(τ) = Tortuosity of path

(μ) = Viscosity of solution

(Δx) = Membrane thickness

It should be noted that the largest leverage to obtaining optimum TMF is the radius of the pores because it is raised to the fourth power. The next largest lever is the porosity or number of such pores/unit area and the effect of the pore radius which is multiplied by the porosity. Functional optimization for this application therefore also relies on achieving a tight standard deviation of pore radius in the effective zone of filtration as well as a high density of such pores in the primary filtration zone of the membrane. The relationship is also affected by temperature to the extent that temperature changes the value of the parameters including the viscosity of the solution.

The membranes of the present invention may be prepared using any suitable polymer fibers which will result in a hollow fiber membrane which meets the biocompatibility requirements and properties of the invention. Such membrane materials and surfaces must be highly biocompatible and resist clotting, protein adhesion and detrimental interaction with immune system components. The structural strength of the hollow fiber membranes must be high enough to safely withstand implantation as well as the hydraulic and physical perturbations existing in the vena cava environment. Thus, the functional convection extraction efficiency of such hollow fibers must be suitable to meet clinical treatment requirements in the smallest possible size in order to fit within the vena cava without stress. The membranes also must be designed with a morphology optimized for blood flow on the outside of the fiber and ultrafiltrate on the inner lumen of the fiber. A number of potentially suitable polymer fiber membrane materials are described in the aforesaid patents including fibers

produced from polyurethane, polypropylene, polyethersulfone, polycarbonate, nylon, polyimide and other synthetic resins known to those skilled in the art. A preferred polymer is polysulfone membrane, and more preferably a polysulfone modified with a polyethylene oxide-polyethylene glycol copolymer. Such polysulfone fibers are produced in the presence of polymer dopes, core fluids, and coagulation fluids using processes including membrane spinning methods which achieve the desired product. Examples of such additive materials used in the polymerization process, spinning process and/or fiber membrane production include polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide, dimethyl sulfoxide, and mixtures of two or more such materials. Such polysulfone fibers have been found to have the least detrimental characteristics that influence protein membrane interaction such as crystallinity, ionic groups, hydrogen bonding groups and hydrophobic sites. The specific method used for producing the aforesaid polymers as well as the processes and parameters during the manufacture are known to those skilled in the art. The general specifications and variation range of parameters for the hollow fiber membranes for medical applications within the scope of the present invention are as follows:

PLASMAPHERESIS APPLICATIONS

PARAMETER	SPECIFICATIONS		RANGE OF APPLICATION	
	FROM	TO	FROM	TO
Outer Diameter µm	735	765	200	800
Inner Diameter µm	240	260	50	700
Wall Thickness µm	175	260	50	600
Zone 1 mean flow pore diameter µm	0.7	0.8	0.3	1
Zone 4 pores @ ID diameter µm	5	40	1	60
Tensile force @ Break Pounds/in^2	750	900	500	1500
Elongation @ Break %	65	80	50	150
Fluid Flux (H_20) ml/min/cm^2 @ 100 mmHg	1.0	1.5	1.0	10
TMF plasma ml/min/cm^2/10 mmHg	.75	4	.5	9

ULTRAFILTRATION APPLICATIONS

PARAMETER	SPECIFICATIONS		RANGE OF APPLICATION	
	FROM	TO	FROM	TO
Outer Diameter µm	450	650	123	750
Inner Diameter µm	250	325	100	700
Wall Thickness µm	150	200	40	400
Zone 1 mean flow pore diameter µm	0.01	0.03	0.005	0.05
Zone 4 pores @ ID diameter µm	5	40	1	60
TMF H_2O ml/min/cm^2/10 mmHg	.75	4	.5	9
Tensile force @ Break Pounds/in^2	700	800	450	1200
Elongation @ Break %	50	65	40	100

Examples of medical applications for which the hollow fiber membranes of the present invention may be used include the following: therapeutic apheresis applications including plasma exchange, cascade protein separation by filtration, cascade protein removal or modification by adsorption cartridge, cryogenic modification, or chemical adaptation; fluid management application or congestive heart failure both acute and chronic; tissue engineering applications including online generation of media for bioreactor from xenogenic, allogenic, and autogenic sources; continuous renal replacement therapy (CRRT) for both acute and chronic kidney failure; edema prevention therapies for MODS (multiple organ dysfunction syndrome); cytokine removal or modification in therapy for septic shock or SIRS (systemic inflammatory response syndrome); plasma extraction from peritoneal ascites; intermittent hemodialysis (IHD) or hemodiafiltration; and ARDS (acute respiratory distress syndrome) therapy by reduction of pulmonary edema and physiological pulmonary dead space.

Additional uses for the specific membranes of the present invention as well as those covered in the aforesaid U.S. patents incorporated herein by reference will be evident to those skilled in the art.

WHAT IS CLAIMED IS:

1. An *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltration membrane comprising:

a plurality of elongated hollow fibers each fiber having an interior lumen extending along the length thereof and a fiber wall having a plurality of zones between the inner and outer wall surfaces, each of said zones having a mass density different than the mass density of an adjacent zone, said fiber wall characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface.

2. A membrane of Claim 1 wherein said membrane fiber wall has two mass density zones.

3. A membrane of Claim 1 wherein said membrane fiber wall has three mass density zones.

4. A membrane of Claim 1 wherein membrane fiber wall has four or more mass density zones.

5. A membrane of Claim 1, 2, 3 or 4 wherein each of said zones is characterized by a different average nominal pore size.

6. A membrane of Claim 5 capable of *in-vivo* plasmapheresis wherein said lower mass density zone is characterized by a nominal average pore diameter of between about 1 µm and about 60 µm.

7. A membrane of Claim 5 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 µm and about 1 µm.

8. A membrane of Claim 6 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 µm and about 1 µm.

9. A membrane of Claim 1 characterized by having the capability of extracting at least 0.75 ml/min/cm^2/mm Hg of blood plasma at trans-membrane pressures of between about 5 and about 20 mm Hg.

10. A membrane of Claim 5 capable of *in-vivo* ultrafiltration wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

11. A membrane of Claim 1, 2, 3 or 4 comprising a polysulfone fiber.

12. A membrane of Claim 11 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

13. A membrane of Claim 11 wherein said polysulfone fiber is produced in the presence of a composition comprising polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide or dimethyl sulfoxide, or mixtures of two or more thereof.

14. A membrane of Claim 13 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

15. An *in-vivo* plasmapheresis or *in-vivo* ultrafiltration membrane comprising a plurality of elongated hollow fibers each fiber having an interior lumen extending along the length thereof and defined by an inner wall surface, wherein the morphology of said fiber wall is asymmetrical between said inner wall surface and the fiber outer wall surface, said fiber wall having a higher mass density adjacent to the outer wall surface and a lower mass density adjacent to said inner wall surface.

16. A membrane of Claim 15 wherein the higher mass density fiber wall is characterized by pores having a smaller average nominal pore size as compared to the average nominal pore size in the lower mass density fiber wall.

17. A membrane of Claim 16 capable of *in-vivo* plasmapheresis wherein said lower mass density is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

18. A membrane of Claim 16 or 17 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

19. A membrane of Claim 16 capable of *in-vivo* ultrafiltration wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

20. A membrane of Claim 19 capable of *in-vivo* ultrafiltration wherein said lower mass density is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

21. A plasmapheresis or ultrafiltration assembly of Claim 1 or 15 including a catheter in direct fluid communication with said interior lumen of said fiber.

22. A plasmapheresis or ultrafiltration assembly of Claim 21 comprising a dual lumen catheter.

23. A plasmapheresis membrane of Claim 6 or 17 having a plasma trans-membrane flux of between about 0.5 and about 9 ml/min/cm^2 @ 10 mm Hg.

24. A plasmapheresis membrane of Claim 1 or 15 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.7 μm and about 0.8 μm.

25. A plasmapheresis membrane of Claim 24 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

26. A plasmapheresis membrane of Claim 25 having a plasma trans-membrane flux of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

27. An ultrafiltration membrane of Claim 1 or 15 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.01 μm and about 0.03 μm.

28. An ultrafiltration membrane of Claim 27 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

29. An ultrafiltration membrane of Claim 28 having a trans-membrane flux (H_2O) of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

30. A method of carrying out *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltration of a patient's blood, comprising:

implanting a filter device within a blood vessel of a patient, said filter device comprising a plurality of elongated hollow fibers each fiber having an interior lumen extending along the length thereof, said fiber wall having an asymmetrical pore size and asymmetrical mass density morphology between

inner and outer fiber wall surfaces wherein the mass density adjacent to said outer wall is greater than the mass density adjacent to said inner wall, and passing blood plasma and toxins through said fiber wall to said interior lumen and directing said blood plasma and toxins from the patient through said interior lumen.

31. A method of Claim 30 wherein said filter device includes a catheter in direct fluid communication with said interior lumen of said fibers, said method including directing said blood plasma and toxins from the patient through said catheter.

32. A method of carrying out *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltration of a patient's blood, comprising:

implanting a filter device within a blood vessel of a patient, said filter device comprising a plurality of elongated hollow fibers each fiber having an interior lumen extending along the length thereof and a fiber wall having a plurality of zones between the inner and outer wall surfaces, each of said zones having a mass density different than the mass density of an adjacent zone, said fiber wall characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface and passing blood plasma and toxins through said fiber wall to said interior lumen and directing said blood plasma and toxins from the patient through said interior lumen.

33. A method of Claim 32 wherein said filer device induces a catheter in direct fluid communication with said interior lumen of said fibers, said method including directing said blood plasma and toxins from the patient through said catheter.

34. A method of Claim 32 wherein said membrane fiber wall has two mass density zones.

35. A method of Claim 32 wherein said membrane fiber wall has three mass density zones.

36. A method of Claim 32 wherein membrane fiber wall has four or more mass density zones.

37. A method of Claim 32, 33, 34, 35 or 36 wherein each of said zones is characterized by a different average nominal pore size.

38. A method of Claim 32 wherein said lower mass density zone is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

39. A method of Claim 32 for carrying out plasmapherisis wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

40. A method of Claim 38 for carrying out plasmapherisis wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

41. A method of Claim 32 comprising extracting at least 0.75 ml/min/cm^2/mm Hg of blood plasma at trans-membrane pressures of between about 5 and about 20 mm Hg.

42. A method of Claim 32 for carrying out ultrafiltration wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

43. A method of Claim 38 for carrying out ultrafiltration wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

44. A method of Claim 38 wherein said membrane has a plasma trans-membrane flux of between about 0.5 and about 9 ml/min/cm^2 @ 10mm Hg.

45. A method of Claim 32 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

46. A method of Claim 45 for carrying out plasmapherisis wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.7 μm and about 0.8 μm.

47. A method of Claim 45 wherein said membrane has plasma trans-membraine flux of between 0.75 and bout 4 ml/min/cm^2/ @ 10mm Hg.

48. A method of Claim 45 for carrying out ultrafiltration wherein said higher mass density is characterized by a nominal average pore of between about 0.01 μm and about 0.03 μm.

49. A method of Claim 32 for carrying out ultrafiltration wherein said membrane has a trans-membrane flux (H_2O) of between about 0.75 and about 4 ml/min/cm^2/ @ 10mm Hg

SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION

Abstract of the Disclosure

An *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltration membrane comprises a plurality of elongated hollow fibers each fiber having an interior lumen extending along the fiber length, the fiber wall having a plurality of zones between the inner and outer wall surfaces, each of the zones having a mass density different than the mass density of an adjacent zone. The fiber wall is characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface.

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DECLARATION - USA PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION; the specification of which is attached hereto;

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56;

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Reynolds Gorsuch**

Inventor's signature Reynolds Gorsuch

Date 3/29/00

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KNOBBE, MARTENS, OLSON & BEAR, LLP
Customer No. 20,995

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TRANSVI.007A PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Gorsuch, et al.
App. No.	:	Unknown
Filed	:	Herewith
For	:	SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION
Examiner	:	Unknown

<u>ESTABLISHMENT OF RIGHT OF ASSIGNEE TO TAKE ACTION</u>
<u>AND</u>
<u>REVOCATION AND POWER OF ATTORNEY</u>

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The undersigned is empowered to act on behalf of the assignee below (the "Assignee"). A true copy of the original Assignment of the above-captioned application from the inventors to the Assignee is attached hereto. This Assignment represents the entire chain of title of this invention from the Inventors to the Assignee.

I declare that all statements made herein are true, and that all statements made upon information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that willful, false statements may jeopardize the validity of the application, or any patent issuing thereon.

The undersigned hereby revokes any previous powers of attorney in the subject application, and hereby appoints the registrants of Knobbe, Martens, Olson & Bear, LLP, 620 Newport Center Drive, Sixteenth Floor, Newport Beach, California 92660, Telephone

(949) 760-0404, **Customer No. 20,995**, as its attorneys with full power of substitution and revocation to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected herewith. This appointment is to be to the exclusion of the inventor(s) and his attorney(s) in accordance with the provisions of 37 C.F.R. § 3.71.

Please use **Customer No. 20,995** for all communications.

TRANSVIVO, INC.

Dated: 4-3-00

By: ____________
Jim Chestnut

Title: President

Address: 1100 Lincoln Avenue, Suite 206
Napa, CA 94558

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United States Patent & Trademark Office

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